DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12-5-07 has been entered.

Claims 1-48 have been cancelled. Claims 49-53 are pending.

Election/Restrictions

Newly submitted claims 49, 50, 51 and 52 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The elected species of invention is SEQ ID NO:132. These claims no longer encompass the elected specie of invention and as such no longer read on the elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 49-52 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted that since the elected specie is not allowable, the Office has not moved on to the next specie (MPEP 803.02).

Rejections Withdrawn

The rejection of claims 1-4, 9-21, 24, 26 and 47-48 under 35 U.S.C. 112, first paragraph is withdrawn based on the cancellation of the claims.

The rejection of claims 1-3, 15-19, 26, 48 stand rejected under 35 U.S.C. 102(e) as being anticipated by Doucette-Stamm et al (US Patent No. 6800744, issued October 5, 2004 with priority to provisional document 60/051,533 filed July 2, 1997) is withdrawn based on cancellation of the claims.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to "immunostimulatory sequences" (ISS) these immunostimulatory sequences are not modified in any manner. The term ISS is a polynucleotide sequence is defined in the specification a polynucleotide sequence that effects and/or contributes to a measurable immune response as measured in vitro, in vivo and or ex vivo (page 11, lines 18-20 of the specification). Measurable immune responses include antigen-specific antibody production, secretion of cytokines, activation or expansion of lymphocyte populations and activation of a Th1-type response (see page 11 lines 20-24 of the specification).

The teachings of the specification are limited to a demonstration that fully modified phosphorothioate oligodeoxynucleotides of SEQ ID NOS: 18, 38 and 59 provide for immunostimulation by means of increased antigen-specific IgG when administered to mice in conjunction with the antigen. The teachings of the specification also indicate that SEQ ID NO:60 is a negative control and lacks an ISS sequence. The ISS activity, if any, of SEQ ID NO:132 either in its modified form or non-modified form is not set forth in the specification as filed. The ISS activity of any non-modified SEQ ID NO is not set forth in the specification as filed. Strictly speaking the response of other disclosed SEQ ID NOS that produce increased levels of INF-gamma and INF-alpha from mixed cell cultures is not necessarily indicative of an immune response. The source of the INF-gamma and INF-alpha produced in response to the ISS sequence is not taught by the specification as filed. It is noted that the only *in vivo* immunostimulatory response studied was the ability to generate antigen-specific IgG antibody. The generation of antibody is admitted by applicants at page 12, to be largely a Th2-like response. Therefore, the data presented in Examples at pages 85-103 of the specification does not demonstrate for the skilled artisan that the response generated was Th1 mediated (as indicated as preferred at page 11 of the specification). No cytotoxic cellular responses were measured. No delayed type-hypersensitivity response measured. No delineation of the subtype of IgG antibody produced was studied and therefore, the skilled artisan cannot conclude that the response was Th1-like or mediated. Further, there is not one assay of any non-modified immunostimulatory sequence and SEQ IDN O:132 in particular that demonstrates any immunostimulatory activity. The art of record establishes that the biological response to the administration of CpG containing oligonucleotides vary, depending upon the mode of administration and the organism (McCluskie et al , Molecular Med, 5(5):287-300, 1999, especially page 296 and Krieg et al, Immunology Today 21(10):521-526, 2000, especially page 524). CpG-ODNs have multiple stimulatory effects on different cells, such as lymphocytes, dendritic cells, macrophages, natural killer (NK) cells and T cells (see page

619 Wohlleben et al, TRENDS in Immunology 22(11):618-626, 2001). As such, the ability of SEQ ID NO:132 or other claimed non-modified ISS-containing CpG oligonucleotide to be "immunostimulatory" to generate a Th1-like immune response alone or versus a Th2-like immune response has not been demonstrated by this specification as filed. The source of the IFN-gamma has not been ascertained to be related to specific immune cells (i.e. the source of the IFN-gamma not identified as T-cell derived). Isolated T cells were not evaluated and T-cell depleted populations were not evaluated for IFN-gamma production. Any Th1-like response to antigen was not evaluated either *in vitro* or *in vivo*. The Th2-like cytokines were not evaluated, the IgG subclass of antibody not evaluated and therefore the skilled artisan can not make a reasonable conclusion regarding the generation of a Th1-type response as opposed to a Th2-type response. Therefore, "immune stimulation" was not measured in any non-modified SEQ ID NOS:18, 38 and 59. Further, a switch in T helper response (i.e. immunomodulate as described at page 12 of the specification) can only be ascertained in a live animal model such as that described by Wohlleben et al *supra* and this specification is devoid of data using known animal models reflective or typical of a Th2-response such that an effective modulation to a Th1 has been demonstrated. Further, Kline et al (Am J. Physiol. Lung Cell Mol. Physiol., 283:L170-L179, 2002; Kline et al J. Immunol, 160:2555-2559, 1998) teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in an animal model (page L172, page 178, paragraph bridging columns 1-2). As such, the ability of CpG's inducing cytokines does not correlate with its ability *in vivo* to demonstrate immunostimulation. Further, Kline et al 2002, teaches that splenocytes from OVA-treated mice did not develop antigen-specific Th1 phenotype. As such, the specification as filed lacks evidence/data that indicates that the claimed ISS nucleic acids (SEQ ID NO:132, modified or non-modified) possesses immunostimulating activity as claimed.

Weiner (J. Leukocyte Biology, 68:456-463, 2000) states that the molecular mechanisms of CpG oligonucletoides' immunostimulatory effects are not yet understood

(see page 461). While the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agarwal et al, Molecular Med, Today, 6:72-81, 2000, especially pp 78-80). Further, the art of record teach that the phosphorothioate analogs are the most potent in immune stimulation (see Zhao et al (Biochemical Pharmacology, 51:173-182, 1996, page 173 (abstract); of record in PTOL-1449) and there is no evidence of record that any sequence that is not fully phosphorothiolated provides for immune stimulation in any model. Zhao et al teaches that modifications unpredictably effect the ability of modified CpG containing oligodeoxynucleotides to provide for immune stimulation as measured by *in vitro* and *in vivo*. As such, there is no evidence of record that the now claimed unmodified SEQ ID NO:132 or any other unmodified ISS has any ISS activity as defined in the specification.

Additionally, the length of the oligonucleotide impacts its ability to induce interferon gamma production in mixed splenocyte cultures. Yamamoto et al (Antisense Research and Development 4:119-122, 1994) teach that immunostimulatory activity of oligonucletoides of 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases and oligonucleotides 16 bases or less in length were not active even if they possessed the palindromic sequence (see abstract). This specification fails to teach that oligonucleotides having the minimal claimed sequence set forth in SEQ ID NO:132 and sequences of up to about 200 nt containing such, are effective immunostimulators as instantly claimed.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to using the claimed invention in the manner contemplated by the specification for the scope of the claimed invention. Applicants have not provided guidance as to the generation of a Th1-response using unmodified sequences. Activity of the elected invention SEQ ID NO:132 is lacking in the specification as filed. In view of the pleotropic effects of CpG's in inducing IFN-gamma in

numerous cell types and the lack of description or data demonstrating either a switch in a antigen-specific Th2 to Th1 response *in vivo* or the generation of an antigen-specific Th1 response *in vitro* or *in vivo*, the specification is not enabled for the now claimed invention directed solely to unmodified ISS sequences. In view of the foregoing art, one skilled in the art would not accept on its face the limited example of 3 fully phosphorothioate modified ISS oligodeoxynucleotides given in the specification as being correlative or representative of immunostimulation by their non-modified counterparts as claimed or generation of a Th1-type response ***per se*** .

Status of the Claims

Claim 53 is rejected. Claims 46-52 are withdrawn from consideration.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645